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Associations between Depressive Symptoms, Cigarette Smoking, and Cardiovascular Health: Longitudinal Results from CARDIA

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Introduction: Depression is associated with increased risk of incident and recurrent cardiovascular disease, while the association between depression and cardiovascular health (CVH) remains unknown. Because the natural course of depression varies widely, different patterns of depression, as well as co-occurring factors such as cigarette smoking, may influence

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this relationship. We examined potential interactions between longitudinal patterns of depression and smoking with CVH.

Methods: Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we modeled trajectories of depression (Center for Epidemiologic Studies Depression Scale scores; Years 5, 10, 15, 20) and smoking (cigarettes/day; Years 0, 2, 5, 7, 10, 15, 20). We calculated a modified American Heart Association (AHA) CVH Score (weight, blood glucose, cholesterol, blood pressure, physical activity, and diet; Year 20); higher scores indicate better CVH. Generalized linear models evaluated associations between depression trajectories, smoking trajectories, and their interaction with CVH Score.

Results: The depression trajectory x smoking trajectory interaction was not associated with CVH Score, but main effects of depression trajectory ($p<.001$) and smoking trajectory ($p<.001$) were observed. Participants with patterns of subthreshold depression ($\beta=-0.26$, $SE=0.08$), increasing depression ($\beta=-0.51$ $SE=0.14$), and high depression ($\beta=-0.65$, $SE=0.32$) had lower CVH Scores than those without depression. Compared to never smokers, participants who quit smoking had higher CVH Scores ($\beta=0.38$, $SE=0.11$), while participants with the greatest smoking exposure had lower CVH Scores ($\beta=-0.49$, $SE=0.22$).

Limitations: CVH Scores were adapted from the AHA guidelines based on the available CARDIA data.

Conclusions: Deleterious depression and smoking trajectories are independently but not synergistically associated with worse CVH.

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Depression is linked to increased risk for incident and recurrent cardiovascular disease (CVD), and adults with a history of depression or elevated depressive symptoms have up to two times greater odds of developing ischemic heart disease or suffering a fatal or nonfatal cardiac event (Van der Kooy et al. 2007; Daskalopoulou et al. 2016; O'Neil et al. 2016). More recently, research has transitioned to evaluating not only risk of developing CVD, but has turned its focus to promoting and maintaining cardiovascular health (CVH). In contrast with standard CVD risk predictors, which rely on non-modifiable demographic factors such as age, sex, and race (e.g., Goff et al. 2014), the 2010 American Heart Association (AHA) guidelines for CVH place less emphasis on non-modifiable factors and focus instead on modifiable lifestyle factors. The seven components of CVH include body weight, blood glucose, total cholesterol, blood pressure, physical activity, diet, and smoking status (Lloyd-Jones et al. 2010), where healthier values of each metric contribute to better (higher) CVH. Beyond the extensive body of research demonstrating an association between depression and increased risk of incident and recurrent CVD, studies are needed to evaluate whether there is also an association between depression and CVH.

Cross-sectional studies have found that adults with depressive symptoms are nearly 2.5 times more likely to have poor, rather than ideal, CVH (Szlejf et al. 2018). However, patterns of depressive symptoms are known to vary widely across the lifespan (Musliner et al. 2016). For some, depressive symptoms may be persistent, while others may go through periods of depression that later resolve. These distinct patterns have been shown to differentially affect physical, psychological, and social functioning, including some cardiovascular-related outcomes (Byers et al. 2012). Together, these findings indicate that it is relevant to evaluate patterns of depressive symptoms to best understand how timing and severity of depressive symptoms may influence CVH. No studies have yet evaluated longitudinal patterns of depression with CVH outcomes.

Many argue that the associations between depression and cardiovascular outcomes can be explained by behavioral factors. For example, depression and smoking are highly comorbid, current and former smokers are more likely to experience depression, and smokers with depression tend to smoke more heavily than smokers without depression (A. E. Taylor et al. 2014; Pratt and Brody 2010). The associations between depression and smoking have been shown to be longitudinal and bidirectional (Chaiton et al. 2009). There is significant overlap in the mechanisms by which depression and smoking are hypothesized to negatively impact CVH (e.g., via inflammatory processes; Penninx 2017; USDHHS 2010). In addition, we previously demonstrated that comorbid exposure to depressive symptoms and cigarette smoking accumulated during the lifespan among otherwise healthy adults had a synergistic association with risk of subclinical CVD (Carroll et al. 2017b), suggesting that smoking exposure may also moderate the influence of depressive symptom patterns on CVH.

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No studies have specifically evaluated the potential interaction between depression and smoking with CVH. The purpose of the present study was to evaluate whether patterns of exposure to depressive symptoms over 20 years predicted CVH in middle adulthood, and whether patterns of exposure to smoking moderated this association. To identify distinct patterns of exposure, we used group-based trajectory modeling (Jones and Nagin 2007; Jones et al. 2001), an application of discrete mixture modeling designed to identify clusters of individuals who follow a similar progression of behavior over time. These patterns allowed us to determine acceleration (increase), deceleration (decrease), and rates of change (trends) in behaviors of interest, and to examine whether these patterns are differentially associated with CVH outcomes. We hypothesized that adults with patterns of high or increasing depressive symptoms and patterns of high or increasing smoking from young to middle adulthood (Year 0 to Year 20) would have synergistically poorer CVH at Year 20 (i.e., lower prevalence of AHA's healthy lifestyle factors), beyond the individual additive effects of greater exposure to depressive symptoms and smoking, compared to adults with patterns of low or decreasing depressive symptoms, smoking, or both. We further examined this relationship exclusively among ever-smokers, with the similar hypothesis that ever-smokers with patterns of high or increasing depressive symptoms and patterns of high or increasing smoking from young to middle adulthood would have synergistically worse CVH at Year 20.

Methods

Study and sample description

The Coronary Artery Risk Development in Young Adults (CARDIA) study (http://www.cardia.dopm.uab.edu/) is an ongoing longitudinal, community-based cohort study designed to evaluate the development of coronary heart disease risk factors during young adulthood. In 1985-1986 (Year 0), 5,115 young adults aged 18-30, who had permanent residence in the recruitment area and were in good health, were recruited from four United States cities (Cutter et al. 1991). Participants were recruited by telephone using census tracts, random digit dialing, health plan data, and household rosters; further details of recruitment and retention strategies have been published elsewhere (Hughes et al. 1987). Recruitment was stratified on sex, race (Black and White), age (18-24 years and 25-30 years), education (≤ high school graduate and > high school graduate), and study site (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Follow-up exams were conducted at Year 2 (N=4,624, ages 20-32), 5 (N=4,352, ages 23-35), 7 (N=4,086, ages 25-37), 10 (N=3,950, ages 28-40), 15 (N=3,672, ages 33-45), 20 (N=3,547, ages 38-50), 25 (N=3,499, ages 43-55), and 30 (N=3,358, ages 48-60). Because the dietary data required to assess CVH were only collected at Year 20 (see Measures: CVH assessment below), only data from Year 0 through Year 20 were included in this secondary data analysis. All procedures were IRB approved at each of the study sites, and informed consent was completed by each participant at each exam.

Measures

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Depressive symptoms. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression scale (CES-D; Radloff 1977) at Years 5, 10, 15, and 20. The CES-D is a 20-item, self-report, global measure of depressive symptoms over the past two weeks. Each symptom is assessed on a scale from 0 (never) to 3 (nearly every day), with total scores ranging from 0 (none/low depressive symptoms) to 60 (high depressive symptoms). Scores ≥16 points are considered to be clinically elevated symptoms.

Smoking. Smoking was queried at each exam (Years 0, 2, 5, 7, 10, 15, and 20), including current smoking status (≥5 cigarettes/week, almost every week) and, if participants indicated that they were a current smoker at any exam, they were then queried as to the average number of cigarettes per day (CPD) they smoked. Participants who attended an exam but reported that they were not currently smoking were noted as smoking 0 CPD for that exam. Some analyses were restricted to ever-smokers, defined as participants who reported current smoking at one or more exams.

CVH assessment. The AHA CVH Score is a clinical assessment of CVH comprising seven health metrics (body weight, blood glucose, total cholesterol, blood pressure, physical activity, diet, and smoking status) (Lloyd-Jones et al. 2010). Though distinct from CVD risk profiles (e.g., Goff et al. 2014), the CVH score is inversely associated with fatal and non-fatal CVD events (Fang et al. 2016). Each component is scored as poor (0), intermediate (1), or ideal (2), yielding an overall score between 0 and 14 (Huffman et al. 2012). This score has been used to evaluate associations between CVH and psychosocial variables, including depressive symptoms (e.g., Szlejf et al. 2018). For the present analyses, because smoking was included as a predictor variable, a modified score was calculated without smoking status for total scores ranging from 0 to 12, where higher scores reflect greater CVH (i.e., greater adherence to healthy lifestyle factors). In sensitivity analyses, the CVH Score was calculated with smoking status (presented in the **Electronic Supplementary Material: Methods, Table 1**).

Body weight. BMI was calculated from the physical exam measurements of weight in kilograms divided by height in meters squared (kg/m^2). The AHA thresholds for the CVH BMI score are: (0) Poor= ≥30 kg/m^2, (1) Intermediate= ≥25 and <30 kg/m^2, and (2) Ideal= <25 kg/m^2. BMI was not calculated for participants who were pregnant at the time of the exam.

Blood glucose. Glycemic status was assessed by fasting blood glucose [FBG] or hemoglobin A1c [HbA1c] levels, self-reported diagnosis of diabetes mellitus, and use of glucose-lowering medications. Participants were instructed to fast for 12 hours and avoid smoking and heavy physical activity for at least 2 hours prior to the exam. FBG was measured by the hexokinase-ultraviolet method. HbA1c was measured by the high-performance liquid chromatography method. The AHA thresholds for the CVH glucose score are: (0) Poor= FBG ≥7 mmol/L, HbA1c ≥48 mmol/mol, or diagnosed with diabetes mellitus (or using medications) with HbA1c ≥53 mmol/mol; (1) Intermediate= FBG ≥5.6 mmol/L and <7 mmol/L, HbA1c ≥39 mmol/mol and <48 mmol/mol, or diagnosed with diabetes mellitus (or using medications) with HbA1c <53 mmol/mol; and (2) Ideal= FBG <5.6 mmol/L, HbA1c <39 mmol/mol, and not diagnosed with diabetes mellitus (and not using medications).

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Total cholesterol. Total cholesterol was determined by enzymatic procedures using the ABA Biochromatic instrument (Warnick 1986) following 12 hours of fasting and at least 2 hours avoiding smoking and heavy physical activity. The AHA thresholds for the CVH cholesterol score are: (0) Poor= total cholesterol ≥240 mg/dL or treated total cholesterol ≥200 mg/dL, (1) Intermediate= total cholesterol ≥200 mg/dL and <240 mg/dL or treated total cholesterol <200 mg/dL, and (2) Ideal= untreated total cholesterol <200 mg/dL.

Blood pressure. Three seated blood pressure (BP; mmHg) measurements were taken after a 5-minute resting period and the 2nd and 3rd readings were averaged. The AHA thresholds for the CVH BP score are: (0) Poor= untreated or treated systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, (1) Intermediate= untreated SBP ≥120 mmHg and <140 mmHg or DBP ≥80 mmHg and <90 mmHg, or treated SBP <140 mmHg and DBP <90 mmHg, and (2) Ideal= untreated SBP <120 mmHg and DBP <80 mmHg.

Physical activity. The AHA thresholds for the CVH physical activity score are: (0) Poor= no leisure-time physical activity (<1 minute/week), (1) Intermediate= ≥1 and <150 minutes/week of moderate intensity or ≥1 and <75 minutes/week of vigorous intensity physical activity, and (2) Ideal= ≥150 minutes/week of moderate intensity or ≥75 minutes/week of vigorous intensity physical activity. In CARDIA, participants completed the physical activity history (PAH) questionnaire, which queries the average amount of time spent engaging in various light, moderate, and vigorous intensity physical activities from which a calculation of "exercise units" (EU) is derived (Jacobs et al. 1989). A direct conversion from the PAH score to the AHA CVH physical activity score was not possible. For Ideal physical activity, ≥300 EU that has been found to be a valid threshold for adults meeting physical activity guidelines (Gabriel et al. 2014). For Intermediate physical activity, we chose a threshold higher than 0 EU because the PAH score includes light intensity activities whereas the AHA CVH Score is calculated only from moderate and vigorous intensity activities. Therefore, the thresholds for the modified physical activity score were: (0) Poor= <150 EU, (1) Intermediate= ≥150 EU and <300 EU, and (2) ≥300 EU.

Diet. The AHA diet recommendations include 5 measures, including ≥4.5 cups/day of fruits/vegetables, ≥2 servings (3.5 oz) of fish per week (3.5-oz servings), <1500 mg/day of sodium, <450 kcal (36 oz)/week of sweets/sugar-sweetened beverages, and ≥3 servings/day of whole grains. Participants completed CARDIA Diet History Interview, from which we derived the diet scores consistent with AHA thresholds, as has been done previously (Liu et al. 1994; McDonald et al. 1991). The thresholds for the AHA CVH diet score were: (0) Poor= meeting 0 or 1 of the AHA diet recommendations, (1) Intermediate= meeting 2 or 3 of the AHA diet recommendations, and (2) Ideal= meeting 4 or 5 of the AHA diet recommendations.

Data analysis

All analyses were conducted using SAS, Version 9.4. A threshold of $p<.05$ (two-sided) was used to determine statistical significance.

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Trajectory modeling. We used latent class models (fitted by SAS Proc Traj; Jones and Nagin 2007; Jones et al. 2001) to model the developmental trajectories for 1) CES-D scores in the full sample, 2) CPD in the full sample, 3) CES-D scores among smokers, and 4) CPD among smokers. CES-D score trajectories used data from Years 5, 10, 15, and 20 using the censored normal (CNORM) model. CPD trajectories used data from Years 0, 2, 5, 7, 10, 15, and 20 using the zero-inflated Poisson (ZIP) model due to the large proportion of 0-values. We analyzed trajectory models with 2 through 10 groups, and model fit was assessed using the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC), as recommended (Nagin et al. 2016; Niyonkuru et al. 2013). The optimal number of trajectory groups is determined when the BIC and AIC were maximized or when adding more groups did not substantially differentiate between trajectory patterns. We then qualitatively assessed the trajectory patterns and determined whether the patterns were clinically meaningful (i.e., unique and interpretable patterns that follow observed population trends). We first ran each model with a cubic function; however, the CES-D trajectories did not reach a global maximum until we assigned lower polynomial function (quadratic). Next, because trajectory models often find only the local maximum (as opposed to the global maximum) when using default start values, we ran each model using the recommended start parameters and polynomial function for each trajectory group to achieve a model that reached a global maximum (i.e., best-fit polynomial function for each trajectory group within the trajectory model; Jones and Nagin 2007). The posterior predictive probability of group membership was calculated for each model, and participants were assigned to the trajectory group for which they had the greatest posterior predictive probability. The average posterior predictive probabilities were assessed for adequacy of model fit (see Electronic Supplemental Material; Niyonkuru et al. 2013). Finally, we named each trajectory group based on qualitative examination of the patterns of depression and smoking.

Missing data. No missing data were imputed for the present analysis. Trajectory modeling allows all participants with at least one measure at any exam to be categorized in the trajectory model. As a result, no participants were excluded from the present analysis due to missing CES-D or CPD data. Likewise, because the covariates included in all models were collected at baseline, none of these data were missing.

Of the 5,115 participants enrolled in CARDIA, 442 (9%) did not complete the CES-D at any exam and were excluded from the trajectory analyses. Of 4,672 participants with complete trajectory data, 1,586 (34%) were missing data on one or more of the CVH measures at Year 20: 1,154 on body weight, 1,177 on blood glucose, 1,124 on cholesterol, 1,132 on blood pressure, 1,151 on physical activity, and 1,532 on diet.

Of the 2017 CARDIA participants who reported any smoking history (ever-smokers), 190 (9%) were missing data on the CES-D. Of 1,827 ever-smokers with complete trajectory data, 739 (40%) were missing data on one or more of the CVH measures at Year 20: 568 on body weight, 659 on blood glucose, 553 on cholesterol, 560 on blood pressure, 568 on physical activity, and 719 on diet.

Primary analyses. Generalized linear models (GLM) were used to examine the associations between CES-D trajectory, CPD trajectory, and the CES-D trajectory x CPD trajectory interaction with

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CVH Score at Year 20. To ensure that power to detect an interaction in a 5x5 interaction analysis was preserved, the analyses were also run with the trajectory group variables entered as continuous measures ranked by increasing levels of exposure. For models with a non-significant interaction term, the interaction term was removed and the main effects of CES-D trajectory or CPD trajectory were examined. As noted above, all models were also completed with the CVH Score calculated with smoking status (see **Electronic Supplementary Material**). Adjusted models included sociodemographic covariates: sex (male, female), race (White, Black), age (years), and educational attainment (years).

Results

Sample characteristics

The 3,086 participants with complete data for analyses in the full sample comprised 57% female, 46% Black, and were 45 years of age (SD=3.6 years) with 15 years of education (SD=2.6 years) at Year 20. Participants excluded from the analysis were more likely to be male (49%), black (59%), have fewer years of education (M=14 years, SD=2.5), reported modestly higher depressive symptoms when available (between 1 and 2 points on the CES-D), and were more likely to be smokers.

The 1,088 ever-smokers with complete data for analysis comprised 56% female, 53% Black, and were 45 years of age (SD=3.6 years) with 14 years of education (SD=2.4 years) at Year 20. Reflective of the full sample, ever-smokers excluded from the analysis were more likely to be male (52%), black (63%), and have fewer years of education (M=13 years, SD=2.3), but they did not differ in CES-D scores or CPD.

The prevalence rates for each CVH Score component (BMI, blood glucose, cholesterol, blood pressure, physical activity level, and diet) in the full sample and among smokers are presented in **Table 1**. The CVH Scores ranged from 0 to 12, with a mean CVH Score of 7.2 (SD=2.2) in the full sample and 7.0 (SD=2.1) among ever-smokers.

Trajectory models

The final trajectory models are presented in **Figure 1**. All trajectory models were best fit using a 5-group model. For CES-D scores in the full sample (**Figure 1a**), the model included trajectories characterized by consistently low scores ("no depression," 57%), persistently moderate scores <16 ("subthreshold depression," 30%), initially high scores that decreased to subthreshold levels ("decreasing depression," 4%), initially subthreshold scores that increased ("increasing depression," 8%), and persistently high scores ("high depression," 1%). Among smokers (**Figure 1b**), the CES-D trajectories revealed similar patterns of no depression (51%), subthreshold depression (29%), decreasing depression (5%), increasing depression (12%), and high depression (2%).

For CPD in the full sample (**Figure 1c**), the model included trajectories characterized by consistent 0 CPD ("nonsmokers," 55%), initial light smoking around 5 CPD that decreased to nearly 0 by Year 5 ("quitters," 14%), smoking that decreased over time from 10 CPD to 5 CPD ("light smokers," 15%),

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smoking that decreased over time from 15-20 CPD to 10 CPD ("moderate smokers," 12%), and persistent, heavy smoking that started at 30-35 CPD and decreased over time to 15-20 CPD ("heavy smokers," 3%). Among smokers (**Figure 1d**), CPD trajectories were characterized by <5 CPD that decreased to near-0 CPD ("quitters," 13%), persistent light smoking around 5 CPD ("light smokers," 24%), persistent smoking around 10 CPD that decreased to around 5 CPD ("moderate smokers," 31%), persistent smoking that decreased from around 20 CPD to between 15 CPD ("heavy smokers," 25%), and persistent smoking that decreased from 30-35 CPD to 20-25 CPD ("very heavy smokers," 7%).

CES-D trajectory x CPD trajectory and modified AHA CVH Score

The mean (standard deviation) CVH Score by each trajectory group are presented in **Electronic Supplementary Material: Table 3**. In the GLM, the CES-D trajectory x CPD trajectory interactions were not significant for either model predicting CVH Score at Year 20 (full sample $p_{interaction}$=.374; smokers $p_{interaction}$=.473; full model results presented in **Table 2**). When the trajectory groups were entered as a continuous variable, we still did not find a significant interaction between the CES-D trajectory x CPD trajectory in either the full sample ($p_{interaction}$=.299) or among smokers ($p_{interaction}$=.430).

After removing the non-significant interaction terms, we observed main effects of both CES-D trajectory (p<.001) and CPD trajectory (p<.001) in the full sample (full model results presented in **Table 3**). Compared to participants in the no depression group (lsmean=7.23), CVH scores were lower among participants in the subthreshold depression group (lsmean=6.96), increasing depression group (lsmean=6.71), and high depression group (lsmean=6.58); the difference between the no depression group and the decreasing depression group (lsmean=7.02) did not reach statistical significance. Among CPD trajectories, only those in the heavy smokers group (lsmean=6.47) had significantly lower CVH Scores than those in the nonsmokers group (lsmean=6.96), while those in the quitters group (lsmean=7.34) had significantly higher CVH Scores; differences between nonsmokers and light smokers (lsmean=6.96) and moderate smokers (lsmean=6.78) did not reach statistical significance.

Among smokers, there was not a main effect of CES-D trajectory (p=.107) but we did observe a main effect of CPD trajectory (p<.001). There was an inverse dose-dependent association between CPD trajectory and CVH Score, where compared to quitters (lsmean=7.45), CVH Scores were lower with greater exposure (moderate smokers lsmean=6.76; heavy smokers lsmean=6.65; very heavy smokers lsmean=6.14); CVH Scores were not significantly lower among light smokers (lsmean=7.27) compared to quitters.

Discussion

Contrary to our hypothesis, the interactions between patterns of depressive symptoms and patterns of smoking from young- to middle-adulthood were not synergistically associated with CVH in middle-adulthood previously among healthy, community-dwelling adults. This finding contrasts with studies demonstrating that depressive symptoms and smoking interact to convey increased risk for developing CVD (Rutledge et al. 2012; Carroll et al. 2017b). However, we observed interesting main

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effects of patterns of depressive symptoms and patterns of smoking. Generally, greater exposure to either depressive symptoms or smoking independently over 20 years was associated with poorer CVH, as assessed by a composite measure based on the AHA's definition of modifiable lifestyle factors (Huffman et al. 2012). These findings may suggest that differential patterns of depressive symptoms and smoking matter less than total, cumulative exposure to these risk factors for maintaining and promoting CVH.

The CARDIA study allowed us to examine longitudinal patterns of depressive symptoms and smoking from young- to middle-adulthood among mostly disease-free individuals with CVH outcomes. Nonetheless, the following discussion should be considered within the context of some limitations. First, as noted above, some of the AHA CVH Score calculations had to be adapted for the CARDIA dataset, which limits our interpretation of CVH and comparisons with results of other studies using the AHA CVH Score. Second, we were constrained by the available data for this secondary analysis, including limited information regarding psychiatric history and antidepressant treatment. Third, discussion of the present results within the context of the available literature is limited by variability in the measurement of depression and depressive symptoms, which has been shown to affect the strength of the associations between depression and CVD risk (Nicholson et al. 2006). Therefore, when possible, the following discussion is limited to those studies with measurement constructs that were similar to those used in the present study. Finally, the lack of an interactive effect between depressive symptoms and smoking may be reflective of limited power to detect an interaction in the present analysis, although sensitivity analyses with the trajectory variables entered continuously to preserve power also did not detect a significant interaction.

In the main effects analyses, we observed an association between patterns of elevated depressive symptoms (subthreshold depression, increasing depression, and high depression) and worse CVH in the full sample in a dose-dependent manner; those with decreasing depression did not differ significantly from those without depression. In other words, those with greater exposure to depression had poorer adherence to healthy lifestyle factors comprising CVH. This pattern was similarly observed in a study which found that, although depressive symptoms among adolescents was associated with greater risk of physical health problems during adolescence and young adulthood, those participants whose adolescent-stage depressive symptoms resolved then had lower risk of physical health problems during young adulthood (Ames and Leadbeater 2018). These results suggest that the physical impact of depressive symptoms may be reversible, particularly with early identification and treatment. It is also possible that the groups with decreasing or increasing depressive symptoms in the present study were too small to detect a significant difference from those without depression.

A small number of studies have also found that individuals with psychological conditions, including depression, have poorer CVH as assessed by the adherence to the AHA CVH guidelines of modifiable lifestyle factors (Veromaa et al. 2017; Kronish et al. 2012; Espana-Romero et al. 2013; Li et al. 2015; Gaye et al. 2016), and numerous studies have established an association between depression and incidence and prevalence of CVD (e.g., cardiac events; Mathur et al. 2016), early CVD conditions (e.g.,

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cholesterol; Davidson et al. 2000; Shin et al. 2008), and other CVD risk conditions (e.g., diabetes; Rotella and Mannucci 2013). In one study among middle-aged adults in Korea using latent growth trajectory modeling of depressive symptoms, trajectories of high depressive symptoms were associated with greater prevalence of metabolic abnormalities over an average of 4 years of follow-up, even after accounting for smoking (Kim et al. 2015). Overall, however, few studies have evaluated patterns of exposure to depressive symptoms with CVH outcomes, which may reveal important information regarding the timing and severity of this risk condition.

A consideration for future studies is that certain clusters of depressive symptoms (e.g., somatic symptoms), rather than a global assessment, may have a greater influence on CVH compared to others, as has been frequently demonstrated among patients with CVD (Baune et al. 2012). A 2017 analysis of CARDIA evaluating the interaction between depressive symptom clusters and smoking found that only somatic symptoms of depression significantly interacted with smoking exposure to predict greater odds of CAC (Carroll et al. 2017a), while a 2012 analysis of CARDIA found that the negative affect cluster was associated with risk of developing CAC more so than somatic symptoms or other symptom clusters (Stewart et al. 2012). Fewer studies have examined this association with incident CVD, but a 2014 study demonstrated that somatic symptoms of depression were associated with incident CAD events (Hawkins et al. 2014). Future studies may also find that specific depressive symptoms are more robustly associated with CVH.

We also observed a main effect of smoking patterns in the full sample. First, compared to never smokers, quitters had significantly better CVH (i.e., greater prevalence of adherence to modifiable lifestyle factors). Of course, it is well established that quitting smoking can lower one's blood pressure and cholesterol levels and improve diabetes management (USDHHS 2014), all factors assessed in the CVH Score. Conversely, those who quit smoking often gain weight (Aubin et al. 2012) which would decrease CVH, although this outcome varies widely and may not have been substantial enough to affect a participant's BMI categorization. Adults who quit smoking are more physically active and, moreover, the disparity in physical activity levels between those who quit smoking and those who continue smoking increases over time (Auer et al. 2014). In addition, quitting smoking has been associated with a lower prevalence of psychiatric conditions, including depression (Piper et al. 2013; G. Taylor et al. 2014), which likely also contributes to improved health behaviors and overall improvements in CVH components, even compared to those who never smoked.

Second, among smokers, greater smoking exposure was associated with worse CVH in a dose-dependent manner compared to never smokers. These findings support public health warnings that continuing to smoke, even at low rates, will adversely affect physical health (USDHHS 2014). Aside from the risk directly attributable to smoking, current smoking is also associated with poor health behaviors comprising CVH as well as other lifestyle factors that adversely affect CVD, such as low medication adherence (Kamran et al. 2014; Al AlShaikh et al. 2016), lower physical activity levels and more time spent sedentary (Noble et al. 2015; Kaczynski et al. 2008), and greater prevalence of substance use and psychiatric disorders (Morisano et al. 2009; Chou et al. 2016). Public health efforts are warranted to

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continue to deter smoking initiation, as are both individual and population-level interventions to help current smokers quit.

Based on our findings, it does not appear that relationship between depression and CVH is moderated by smoking status. It remains possible that other risk behaviors, such as a sedentary lifestyle, limited physical activity, or poor diet, or a combination of behavioral factors, are mechanisms through which depression influences CVH (Liu et al. 2017; Penninx 2017). It has also been hypothesized that depression negatively impacts CVH via other treatable cardiovascular and metabolic conditions (Hackett and Steptoe 2016; Kim et al. 2015). A recent study with over 10,000 healthy adults followed for 20 years similarly did not find that depressive symptoms significantly interacted with hypertension, dyslipidemia, or diabetes, to predict cardiac events (Hamieh et al. 2018). The nature of the relationships between depression, treatable cardiovascular conditions, and maintaining CVH remains an area for future research.

There are also studies demonstrating that depression is accompanied by physiological changes in the body, which may lead to CVD. One of the most prominent is the inflammation hypothesis of depression (Berk et al. 2013). In fact, in a previous analysis, we found that the high exposure and increasing patterns of depressive symptoms were associated with inflammation, independent of the smoking patterns (Carroll et al. 2019; Epub ahead of print). Others have shown that the combination of depressive symptoms and inflammation, more than either factor alone, was associated with greater risk of CVD-related mortality among men (Lawes et al. 2018), suggesting the relationship between depressive symptoms and inflammation may be additive rather than mechanistic. There is also evidence for reverse causation, where individuals with other CVD risk factors have been shown to be at risk of depression later in life (Armstrong et al. 2017; Patel et al. 2018). Further studies are needed to fully elucidate the mechanism by which depression increases risk for CVD in order to treat these at-risk individuals and preserve CVH.

The AHA has recently increased its focus on CVH maintenance and promotion, as assessed using modifiable lifestyle factors. In contrast with previous findings of CVD risk development (Carroll et al. 2017b), we did not find that specific patterns of depressive symptoms and smoking had synergistic associations with CVH, as assessed by a composite score of healthy lifestyle factors consistent with the AHA guidelines for CVH (Huffman et al. 2012; Lloyd-Jones et al. 2010). These results suggest that the interaction between depressive symptoms and smoking may be more robust for CVD development than for CVH maintenance. Independently, greater exposure to depressive symptoms and cigarette smoking throughout young- to middle-adulthood were associated with worse CVH, particularly those with higher levels of ongoing exposure to these risk factors. Thus, the pattern of exposure to depression, smoking, and their co-occurrence may be less relevant than total, cumulative exposure over time.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Table 1. Prevalence of modified AHA CVH Score components by score at Year 20: CARDIA, 2005-2006

	Full sample (N=3086)	Ever-smokers (N=1088)
CVH Component	N (%)	N (%)
BMI		
2	880 (29%)	306 (28%)
1	1035 (34%)	369 (34%)
0	1171 (38%)	413 (38%)
Blood glucose		
2	1812 (59%)	621 (57%)
1	1065 (35%)	379 (35%)
0	209 (7%)	88 (8%)
Total cholesterol		
2	1760 (57%)	619 (57%)
1	1171 (38%)	406 (37%)
0	155 (5%)	63 (6%)
Blood pressure		
2	1804 (58%)	588 (54%)
1	1034 (34%)	388 (36%)
0	248 (8%)	112 (10%)
Physical activity		
2	1424 (46%)	478 (44%)
1	742 (24%)	273 (25%)
0	920 (30%)	337 (31%)
Diet		
2	142 (5%)	38 (3%)
1	1627 (53%)	494 (45%)

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0	1317 (43%)	556 (51%)

The thresholds for the modified AHA CVH Score assignment for each component are as follows, where higher scores indicate better CVH: BMI score 2: <25 kg/m^2, 1: 25-30 kg/m^2, 0: >30 kg/m^2. Blood glucose score 2: FBG<7 mmol/L, HbA1c <38 mmol/mol, and not diagnosed with diabetes; 1: FBG 5.6-7 mmol/L, HbA1c 39-48 mmol/mol, or HbA1c <53 mmol/mol and diagnosed with diabetes; 0: FBG ≥7 mmol/L, HbA1c ≥48 mmol/mol, or HbA1c ≥53 mmol/mol and diagnosed with diabetes. Total cholesterol score 2: untreated <200 mg/dL; 1: untreated 200-239 mg/dL or treated <200 mg/dL; 0: untreated >240 mg/dL or treated >200 mg/dL. Blood pressure score 2: <120/<80 mmHg; 1: 120-139/80-90 mmHg; 0: >140/>90 mmHg. Physical activity score 2: ≥300 EU; 1: ≥150 EU and <300 EU; 0: <150 EU. Diet score 2: 4-5 diet recommendations; 1: 2-3 diet recommendations; 0: 0-1 diet recommendations.

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Table 2. Models predicting modified AHA CVH Score at Year 20 based on trajectories of depressive symptoms, smoking, their interaction, and covariates (Years 0 to 20): CARDIA, 1985-2006

Variable	Estimate	95% CI	*p*-value
Full sample (N=3086)			
Intercept	**9.44**	**(8.41 10.47)**	**<.001**
Sex (female)	**-0.31**	**(-0.46 -0.17)**	**<.001**
Race (Black)	**-1.23**	**(-1.39 -1.07)**	**<.001**
Age	**-0.07**	**(-0.09 -0.05)**	**<.001**
Education	**0.12**	**(0.09 0.15)**	**<.001**
CES-D trajectory (ref: no depression)			**0.103**
Subthreshold depression	**-0.34**	**(-0.56 -0.12)**	**0.003**
Decreasing depression	-0.38	(-0.91 0.15)	0.164
Increasing depression	**-0.94**	**(-1.38 -0.51)**	**<.001**
High depression	-0.14	(-1.10 0.83)	0.783
CPD trajectory (ref: nonsmokers)			**0.049**
Quitters	0.29	(0.00 0.57)	0.051
Light smokers	-0.21	(-0.49 0.08)	0.152
Moderate smokers	-0.19	(-0.52 0.13)	0.238
Heavy smokers	**-0.61**	**(-1.20 -0.03)**	**0.040**
CES-D x CPD			0.374
Among smokers (N=1088)			
Intercept	**10.49**	**(8.80 12.17)**	**<.001**
Sex (female)	-0.15	(-0.39 0.08)	0.206
Race (Black)	**-1.14**	**(-1.40 -0.88)**	**<.001**
Age	**-0.07**	**(-0.11 -0.04)**	**<.001**
Education	**0.08**	**(0.03 0.14)**	**0.002**
CES-D trajectory (ref: no depression)			0.178

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Subthreshold depression	-0.09	(-0.80	0.61)	0.796
Decreasing depression	-0.29	(-2.02	1.44)	0.745
Increasing depression	-1.01	(-2.50	0.47)	0.181
High depression	**-2.89**	**(-5.58**	**-0.20)**	**0.035**
CPD trajectory (ref: quitters)				**<.001**
Light smokers	-0.43	(-0.98	0.11)	0.119
Moderate smokers	**-0.75**	**(-1.26**	**-0.24)**	**0.004**
Heavy smokers	**-0.66**	**(-1.20**	**-0.12)**	**0.018**
Very heavy smokers	**-1.37**	**(-2.11**	**-0.62)**	**0.000**
CES-D x CPD				0.473

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Table 3. Models predicting modified AHA CVH Score at Year 20 based on trajectories of depressive symptoms, smoking, (interaction term removed), and covariates (Years 0 to 20): CARDIA, 1985-2006

Variable	Estimate	95% CI		*p*-value
Full sample (N=3086)				
Intercept	**9.37**	**(8.35**	**10.40)**	**<.001**
Sex (female)	**-0.31**	**(-0.45**	**-0.16)**	**<.001**
Race (Black)	**-1.23**	**(-1.38**	**-1.07)**	**<.001**
Age	**-0.07**	**(-0.09**	**-0.05)**	**<.001**
Education	**0.12**	**(0.09**	**0.15)**	**<.001**
CES-D trajectory (ref: no depression)				**<.001**
Subthreshold depression	**-0.26**	**(-0.43**	**-0.10)**	**0.001**
Decreasing depression	-0.20	(-0.57	0.17)	0.281
Increasing depression	-0.51	(-0.79	-0.23)	**<.001**
High depression	-0.65	(-1.27	-0.02)	**0.042**
CPD trajectory (ref: nonsmokers)				**<.001**
Quitters	**0.38**	**(0.16**	**0.59)**	**<.001**
Light smokers	0.00	(-0.21	0.21)	0.976
Moderate smokers	-0.18	(-0.41	0.05)	0.132
Heavy smokers	**-0.49**	**(-0.93**	**-0.06)**	**0.027**
Among smokers (N=1038)				
Intercept	**10.41**	**(8.74**	**12.08)**	**<.001**
Sex (female)	-0.17	(-0.40	0.07)	0.169
Race (Black)	**-1.12**	**(-1.38**	**-0.87)**	**<.001**
Age	**-0.07**	**(-0.11**	**-0.04)**	**<.001**
Education	**0.09**	**(0.04**	**0.14)**	**<.001**
CES-D trajectory (ref: no depression)				0.107
Subthreshold depression	-0.25	(-0.52	0.02)	0.069

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Decreasing depression	0.06	(-0.47	0.58)	0.835
Increasing depression	-0.12	(-0.49	0.25)	0.533
High depression	**-0.89**	**(-1.69**	**-0.10)**	**0.028**
CPD trajectory (ref: quitters)				**<.001**
Light smokers	-0.18	(-0.58	0.22)	0.374
Moderate smokers	**-0.70**	**(-1.08**	**-0.31)**	**<.001**
Heavy smokers	**-0.81**	**(-1.21**	**-0.40)**	**<.001**
Very heavy smokers	**-1.32**	**(-1.88**	**-0.75)**	**<.001**

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Figure Captions

Fig. 1

a. Trajectory model of CES-D scores, full sample (N=3,086). No depression (n=1762, 57%). Subthreshold depression (n=923, 30%). Decreasing depression (n=125, 4%). Increasing depression (n=234, 8%). High depression (n=42, 1%): CARDIA, 1990-2006

b. Trajectory model of CES-D scores, among ever-smokers (N=1,088). No depression (n=555, 51%). Subthreshold depression (n=319, 29%). Decreasing depression (n=56, 5%). Increasing depression (n=134, 12%). High depression (n=24, 2%): CARDIA, 1990-2006

c. Trajectory model of cigarettes per day, full sample (N=3,086). Nonsmokers (n=1707, 55%). Quitters (n=440, 14%). Light smokers (n=466, 15%). Moderate smokers (n=382, 12%). Heavy smokers (n=91, 3%): CARDIA, 1985-2006

d. Trajectory model of cigarettes per day, among ever-smokers (N=1,088). Quitters (n=137, 13%). Light smokers (n=261, 24%). Moderate smokers (n=341, 31%). Heavy smokers (n=274, 25%). Very heavy smokers (n=75, 7%): CARDIA, 1985-2006

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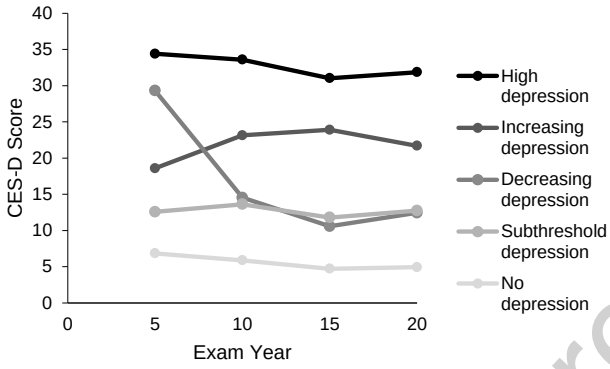
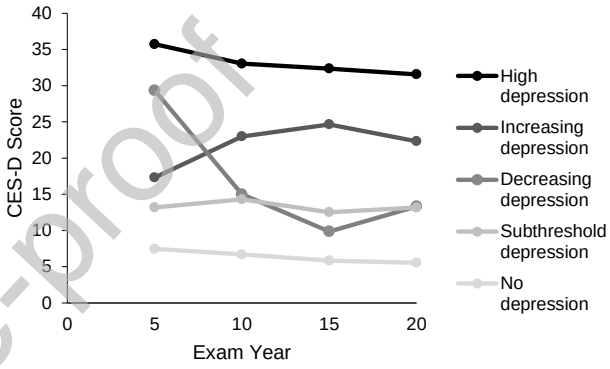
a.



b.



c.

d.

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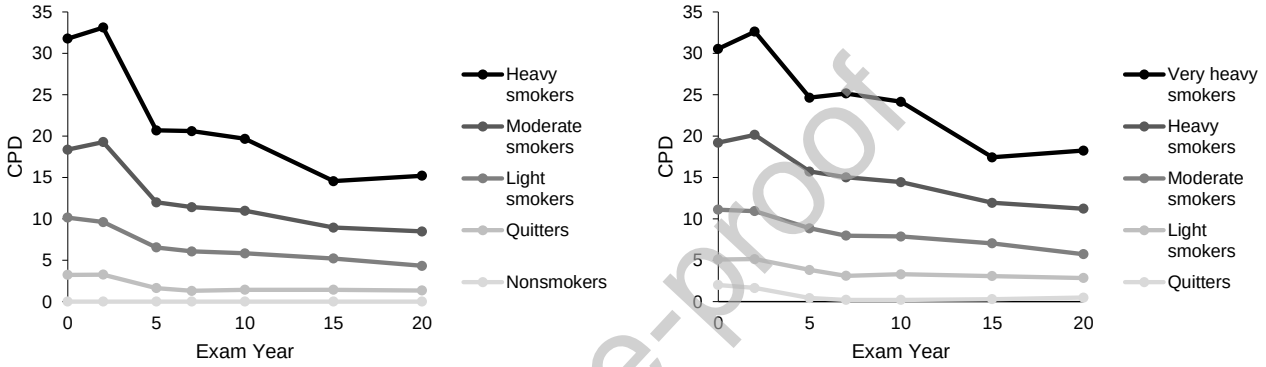

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